

We claim:

1. A method to prepare a hybrid modular polyketide synthase (PKS) from individual modules which method comprises

providing at least a first naturally occurring extender module comprising an ACP domain and a second naturally occurring extender module comprising a KS domain which is downstream of the ACP domain in a naturally occurring PKS,

wherein the C-terminus of said ACP domain is covalently linked to the N-terminus of a naturally occurring intrapolyptide linker (RAL) or interpolyptide linker (ERL) and the N-terminus of said KS domain is covalently linked to the C-terminus of said RAL or ERL, and

wherein either said first module or second module is not covalently linked to said RAL or ERL in a naturally occurring polyketide synthase.

2. A method of preparing a polyketide using the hybrid PKS of claim 1, comprising the steps of preparing a polyketide intermediate using the first module and transferring said intermediate to the second module.

3. The method of claim 1, wherein the ACP domain of the first module is from a first PKS and the entire second module is from the same PKS.

4. The method of claim 1, wherein the entire first module is from a first PKS and the KS domain of the second module is from the same PKS.

5. The method of claim 1, wherein the first and second module each comprise a KS; AT; 0, 1, 2, or 3  $\beta$ ketomodifying ( $\beta$ KM) domains; and an ACP domain wherein the KS and ACP domains are from a first PKS and the AT and  $\beta$ KM domains are from a different PKS.

6. A polyketide synthase prepared by the method of claim 1.

7. The PKS of claim 6, wherein said RAL is selected from the group consisting of M2 *ery*, M4 *ery*, M6 *ery*, M2 *rif*, M3 *rif*, M5 *rif*, M3 *rap*, M4 *rap*, and M7 *rap* intrapolyptide module linkers (SEQ. ID. NO's: 18-26, respectively).
8. The PKS of claim 6, wherein the ERL is selected from the group consisting of M3 *ery*, M5 *ery*, M4 *rif*, M7 *rif*, M8 *rif*, M9 *rif*, M5 *rap*, and M11 *rap* interpolyptide linkers (SEQ. ID. NO's: 27-34, respectively).
9. The PKS of claim 6, wherein said first module comprises the ACP domain of *ery* module 4 and said second module comprises the KS domain selected from the group consisting of *ery* module 5 and 6.
10. The PKS of claim 6, wherein said first module comprises the ACP domain of *ery* module 2 and said second module comprises the KS domain selected from the group consisting of *ery* module 3 and 5.
11. The method of claim 1, wherein the C-terminus of said provided ACP domain is linkerless and then is covalently linked to the N-terminus of a naturally occurring intrapolyptide linker (RAL) or interpolyptide linker (ERL).
12. A PKS prepared by the method of claim 11.
13. The PKS of claim 12, wherein said first module comprises the linkerless ACP domain of *ery* module 4 and said second module comprises the KS domain selected from the group consisting of *ery* module 5 and 6.
14. The PKS of claim 12, wherein said first module comprises the linkerless ACP domain of *ery* module 2 and said second module comprises the KS domain from *ery* module 6.
15. The PKS of claim 12, wherein the said first module comprises the linkerless ACP domain of *ery* loading didomain (LDD) and said second module comprises the KS domain selected from the group consisting of *ery* module 2 and 6.
16. A method to prepare a hybrid modular polyketide synthase (PKS) from individual modules which method comprises

providing at least a first naturally occurring extender module comprising an ACP domain and a second naturally occurring extender module comprising a KS domain which is not normally downstream of the ACP domain in a naturally occurring PKS,

wherein the C-terminus of said ACP domain is covalently linked to the N-terminus of a naturally occurring intrapoly peptide linker (RAL) or interpoly peptide linker (ERL) and the N-terminus of said KS domain is covalently linked to the C-terminus of said RAL or ERL, and

wherein either said first or second module is not covalently linked to said RAL or ERL in a naturally occurring polyketide synthase.

17. A method of preparing a polyketide using the hybrid PKS of claim 16, comprising the steps of preparing a polyketide intermediate using the first module and transferring said intermediate to the second module.

18. The method of claim 16, wherein the ACP domain of the first module is from a first PKS and the entire second module is from the same PKS.

19. The method of claim 16, wherein the entire first module is from a first PKS and the KS domain of the second module is from the same PKS.

20. The method of claim 16, wherein the first and second module each comprise a KS; AT; 0, 1, 2, or 3  $\beta$ ketomodifying ( $\beta$ KM) domains; and an ACP domain wherein the KS and ACP domains are from a first PKS and the AT and  $\beta$ KM domains are from a different PKS.

21. A PKS prepared by the method of claim 16.

22. The PKS of claim 21, wherein said first module comprises the ACP domain of *ery* module 4 and said second module comprises the KS domain selected from the group consisting of *ery* module 2 and 3.

23. The method of claim 16, wherein the C-terminus of said provided ACP domain is linkerless and then is covalently linked to the N-terminus of a naturally occurring intrapolyptide linker (RAL) or interpolyptide linker (ERL).
24. A PKS prepared by the method of claim 23.
25. The PKS of claim 24, wherein the said first module comprises the linkerless ACP domain of *ery* module 4 and said second module comprises the KS domain from *ery* module 2.
26. The PKS of claim 24, wherein the said first module comprises the linkerless ACP domain of *ery* module 2 and said second module comprises the KS domain from *ery* module 2.
27. A method to prepare a hybrid nonribosomal peptide synthetase-modular polyketide synthase (NRPS-PKS) from individual modules which method comprises  
providing at least a first naturally occurring extender module comprising a peptidyl carrier protein (PCP) domain from a naturally occurring NRPS and a second naturally occurring extender module comprising a KS domain from a PKS,  
wherein the C-terminus of said PCP domain is covalently linked to the N-terminus of a naturally occurring intrapolyptide linker (RAL) or interpolyptide linker (ERL) and the N-terminus of the KS domain is covalently linked to the C-terminus of said RAL or ERL, and  
wherein either said first or second module is not covalently linked to said RAL or ERL in a naturally occurring NRPS or PKS.
28. A method of preparing a peptide-polyketide using the hybrid NRPS-PKS of claim 27, comprising the steps of preparing a peptide intermediate using the first module and transferring said intermediate to the second module.
29. A hybrid NRPS-PKS prepared by the method of claim 27.

30. The hybrid NRPS-PKS of claim 29, wherein said RAL is selected from the group consisting of M2 *ery*, M4 *ery*, M6 *ery*, M2 *rif*, M3 *rif*, M5 *rif*, M3 *rap*, M4 *rap*, and M7 *rap* intrapolyptide linkers (SEQ. ID. NO's: 18-26, respectively).
31. The hybrid NRPS-PKS of claim 29, wherein the ERL is selected from the group consisting of M3 *ery*, M5 *ery*, M4 *rif*, M7 *rif*, M8 *rif*, M9 *rif*, M5 *rap*, and M11 *rap* interpolypeptide linkers (SEQ. ID. NO's: 27-34, respectively).
32. The hybrid NRPS-PKS of claim 29, wherein said first module comprises the PCP domain of NovH and said second module comprises the KS domain selected from the group consisting of *ery* module 2 and 6.